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THE ROLE OF DRUGS IN THE TREATMENT OF LEARNING DISABILITY IN CHILDHOOD.

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THIS PAPER ATTEMPTS TO REVIEW THE STATUS OF DRUGS IN THE AREA OF LEARNING DISABILITY. THE PEDIATRICIAN'S TRAINING MUST INCLUDE EXPOSURE TO PRACTICAL AND THEORETICAL PROBLEMS OF LEARNING. OF INTEREST TO THE PEDIATRICIAN IS THE USE OF DRUGS WHICH MODIFY LEARNING RESPONSES. THESE DRUGS ARE CLASSIFIED AS GENERAL STIMULANTS, SPECIFIC STIMULANTS, ANTIDEPRESSANTS, TRANQUILLIZERS, ANTICONVULSANTS, AND RNA STIMULANTS. CAFFEINE IS AN EXAMPLE OF A GENERAL STIMULANT. THE USE OF AMPHETAMINE, A SPECIFIC STIMULANT, IS ILLUSTRATED BY FOUR CASE HISTORIES. THE RESULTS OF THE ADMINISTRATION OF METHLYPHENIDATE, PHENMETRAZINE, RESERPINE, AND DIPHENYLHYDANTOIN ARE REPORTED. IN EACH OF THE BROAD CATEGORIES, THE MEDICATION IS DESIGNED TO CORRECT AN ABERRANT PATTERN OF THE CENTRAL NERVOUS SYSTEM. REFERENCES ARE INCLUDED. THIS PAPER WAS PRESENTED AT THE ASSOCIATION FOR CHILDREN WITH LEARNING DISABILITIES CONFERENCE (BOSTON, FEBRUARY 1968). (BK)

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THE ROLE OF DRUGS IN THE TREATMENT OF LEARNING DISABILITY IN CHILDHOOD

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Historically, the pediatrician has played the role of preventative physician in the areas of infectious disease, nutritional disease, metabolic disease, and mental illness. With an impressive record of accomplishment in these areas, it is only appropriate that he should now extend his interests to the area of learning. Certainly the impact of inadequate learning or learning disability on society can be felt in many directions. If one can use the word "disease" in this context it is apparent that, as in physical illnesses, there are the parallel problems of the individual's illness and its impact on the community. One need not detail the effect on the health of the individual of not being able to learn, nor does one have difficulty in estimating the public health challenge of learning disability.

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Therefore, our task is to explore how the pediatrician can play an effective role in the area of learning disability. As in every disease with which the physician is confronted, the first step is a knowledge and sensitivity of the syndrome. Pediatricians with extended practice experience can testify to the frequency with which patients present with the complaint of school difficulty. However, it is also true that many parents hesitate to come to the pediatrican with these complaints. They hesitate because they are impressed by how busy the pediatrician seems, or because they may not feel that this is properly his area of interest.

The training of the pediatrician must, therefore, include exposure to the practical and theoretical problems of learning. This is a logical extension of his training in child development. He must be able to sense clues of distress in the area of learning as he takes a history on the development of a child and communicates to the parents and to the child his interest and concern in this area. Just as he may play the role of the primary physician, collating the reports of multiple specialists and putting them in perspective for the individual child, he may accomplish the same service in the learning disability. His perspective of the child's genetic, paranatal and neonatal history, plus his knowledge of the family unit, make him uniquely capable of bringing together the impressions of specialists in learning disability (i.e., teachers, psychologists, neurologists, etc.). He may be the best qualified to guide the family in selecting the appropriate remedial program.

Of particular interest to the pediatrician is the use of drugs in the management of learning disability. There are exciting new possibilities in the pharmacology of learning. We have attempted to classify the drugs used in modifying learning response into six general categories: general stimulants; specific stimulants; anti-depressants; tranquillizers; anti-convulsants; and RNA stimulants.

The first class of drugs, the general stimulants, would include such preparations as caffeine. Goodman and Gillman describe the central effects of caffeine as follows:

> "Caffeine stimulates all portions of the cortex, but its main action is on the psychic and sensory functions. It produces a more rapid and clearer flow of thought, and one is capable of a more sustained intellectual effort and a more perfect association of ideas."[1]

This substance therefore awakens the total responsiveness of the individual and will affect his ability to absorb, retain and retrieve information. In this culture, the short term use of such a general stimulant to enhance learning is part of our daily experience.

The amphetamines which many a college student has employed as a learning aide can be included in such a category, but there is an overlap into the next classification of specific stimulants. In this

latter grouping, amphetamines are significant for their paradoxical effect on the "hyperkinetic behavior syndrome". This syndrome, characterized by chaotic, impulsive, disruptive behavior, short attention span, poor concentration, typically results in poor relationships in school, and consequently poor learning. It becomes a learning emergency, in that failure to treat it in the early years of school may result in irretrievable loss.

In 1937,[2] Bradley published his observations of the paradoxical response of children to amphetamine. The application of his observations to the management of the hyperkinetic behavior syndrome has been extensively studied and reported, and has stood the test of controlled studies and long term experience.[3,4,5] The drug purportedly acts upon the reticular activating system of the brain stem. It has its paradoxical effect up through the age of puberty. In general, the "organizational" effect of amphetamine will revert to its general stimulant properties when the reticular system matures. The response to the drug can be so dramatic that some have used the drug response as a diagnostic tool in itself. Controlled studies, as well as clinical observations, have established that in this limited group of children learning clearly improves---school grades go up, retention and retrieval improve.

Four case histories are presented to illustrate the use of amphetamine. Case One was a nine year old boy referred to the clinic

from the school because his hyperactivity in class was sc severe that he was unable to participate in the scheduled school programs. He was in an opportunity class and had a Binet I.Q. of 76. His school placement was ungraded. He was placed on dextro-amphetamine, 5 mgm. twice a day, and showed some improvement. The drug was increased to a level of 45 mgm. a day over a period of a few months and he was sustained on this level for a period of 2 years with consistent improvement in behavior, making it possible for him to participate in the scheduled program of the ungraded class. There was no change in his I.Q. during this time. However, he remained in school on this medication. At the end of approximately 2 years' therapy the effectiveness of the drug seemed to be less, and he was switched to Methylphenidate, 10 mgm. twice a day, from which he received the same beneficial results as had been observed with the dextro-ampetamine.

Case Two, a 10 year old boy from a rural community, one of a family of five children who was referred because of extreme hyperactive behavior and failing school performance. He was notable in his family setting for the marked contrast between his response and those of the family unit, which tended to function as a somewhat stereotyped quiet, passive, rural personality. On 5 mgm. of dextro-amphetamine twice a day, his school performance became all "A's" and "B's", and his performance at home in the family setting became identical to that of his siblings and parents. His drug level was maintained for a period of two years with no change in the response and no apparent need for increase in dosage.

Case Three, a four year old child, was presented to the clinic with a story of extremely uncontrolled behavior, outbursts of temper, disrupting the household and disturbing the nursery school class. She was included in a double-blind drug study of methylphenidate and dextro-amphetamine and placebo and had a dramatic response to medication with a total cessation of her symptoms according to both parents and neighbors. However, on breaking the code, it was found that she was indeed on placebo. She did well on placebo for a period of two months following the study.

Case Four, an eleven year old boy who was known to have an I.Q. in the range of 125, was thrown from a horse and sustained a cerebral laceration with hemi-paresis, loss of speech, and an abnormal electroencephalogram following the injury. When he had recovered sufficiently from his injury to return to school a few months later, he was having severe difficulty in concentrating on the work, he had short attention span, and on testing, was performing on a level of approximately a 105 I.Q. A trial of dextro-amphetamine, 5 mgm. twice a day, was instituted with general improvement in his performance and concentration. At the end of two years, his electroencephalogram was returning to normal, his neurological signs were returning to normal, and his testing revealed that his I.Q. was back up to the level at which it had been before the accident. The drug was discontinued with no ill effects.

In each of the above four case histories, there is a pertinent example of the use of the central nervous stimulant to manage the hyperkinetic behavior disorder. The following observations can be made:

1. There is no correlation with I.Q.

2. Long term drug therapy can be effective.

3. Very high doses of dextro-amphetamine may be appropriate, although equally good effects may be obtained on low dosage in other individuals.

4. Acute brain injury, whose prognosis in uncertain, may be benefited by the use of the drug insofar as the distractibility and short attention span, symptomatic of the injury, can be alleviated during the stages of spontaneous healing.

5. Finally, the obvious need for double-blind studies is demonstrated by the response to the placebo in the case mentioned.

Methylphenidate has been used in the hyperkinetic syndrome, as has amphetamine, and has produced the same dramatic improvement.[6] It is of special interest in that there is a significant number of children who do not respond to amphetamine even though their clinical picture is typical of the hyperkinetic behavior syndrome but who do

respond to methylphenidate. This phenomenon raises the question of biochemical differences and opens opportunities for research into the mechanisms of the action of these drugs.

Phenmetrazine represents two modes of action:[7] it is a significant stimulant, and may function much as amphetamine and methylphenidate, but also is classified among the anti-depressants. This latter classification of drugs has an indirect role on the problem of learning disability. If one accepts the premise that an individual with clinical depression will have diminished facility for learning along with general toxicity of the disease, then it is probable that a drug which relieves the symptoms of depression will improve that individual's ability to learn. Of even more interest is the fact that recent data indicate a biochemical change in anxiety neuroses, as reported by Pitts and McClure in their studies of lactate metabolism.[8] As the use of other drugs in the class of anti-depressants is explored in the light of these biochemical changes, further insight in the dynamics of drug action on central nervous system function will be obtained. The monamine oxidase inhibitors such as Tranylcypromine,[9] the iminodibenzyls such as imipramine,[10] the phenothiazines,[11] all have been used with clinical success in the treatment of depression. Studies which have attempted to show the effect of these drugs on learning have in common the fact that any change in learning skill attributable to the drug can only be based on the drug's general effect on the depressive symptoms.

The tranquillizers present another classification of drugs and such classical examples as reserpine and meprobamate, and chlorodiazepoxides,[12] have all been reported to affect learning skills. As in the anti-depressants, this effect appears to be a non-specific one.

The anti-convulsants, such as diphenylhydantoin,[13] have been reported to have profound effect on central nervous system organizational processes, and considerable energy is being spent to explore this drug's effect on learning disorder. It is speculated that there are sub-clinical seizure equivalents which cause disorganization of normal behavioral and learning processes. The use of the anti-convulsants to control these sub-clinical "seizures" would theoretically result in more effective behavior and learning.

In each of the above five classifications there is a common characteristic---in each, the medication is designed to correct an aberrant pattern of the central nervous system. Whether this be a biochemical defect, inherited or acquired, the goal is to establish the norm. The profound changes that these drugs make on the aberrant nervous system will provide clues as to the nature of the biochemical dynamics of brain physiology and therefore of learning.

An even more provocative area of drug therapy provides the sixth classification, this is the stimulation of RNA synthesis. A number

of studies have proposed that the RNA system contains the basis of learning. Experiments have been presented in which the RNA of a trained animal's brain has been injected into the naive animal, and the naive animal learns a similar task faster than the control. This has been done in planaria and in rats independently by both Babich[14] and Fjerdingstad.

In basic studies of brain physiology substances have been isolated which specifically stimulate the growth of nerve cells. Levi-Montalcini[15] has reported a nerve growth stimulator which, when given to newborn rats, will increase the number of sympathetic nuclei many-fold. Hyden[16] has shown an increase in RNA production in nerve cells of rabbits by the MAO inhibitor Tranylcypromine and the anti-depressant Imipramine.

The drug Magnesium Pemoline, which was originally presented as a central nervous system stimulant, has been reported to increase RNA polimerase activity two to three times in rats.[17] The data are now controversial, but this may represent an area of further study. Behavorial studies in rats have provided suggestive data that Magnesium pemoline treated rats learn better than control.[18] Human trials of the drug are still controversial.[19]

We have attempted to give a kaleidoscopic view of the present status of drugs in the area of learning disability. In terms of

immediate clinical application, the most significant results are those obtained in the use of amphetamines and methylphenidate in the treatment of the learning disability secondary to the hyperkinetic behavior syndrome. With careful study, other stimulants, anti-depressants, tranquillizers and anti-convulsants may prove to affect learning insofar as they alter brain metabolism. In the child with mental retardation or "brain damage" some of these drugs might provide alternate pathways or stimulate defective centers, as is postulated in the action of the amphetamines. These questions remain to be answered. To be able to stimulate RNA synthesis in the same individual may be the ultimate goal.

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